## Special Populations

**Table 5. Special Populations[1-3]**

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Fluticasone/ salmeterol | No dosage adjustment required, in the elderly.<br><br>No dose adjustment required in children for the HFA formulation.<br><br>The Diskus formulation requires dose adjustment in children.<br><br>The Diskus formulation is approved in children 4 years of age and older.<br><br>The HFA formulation is approved in children 12 years of age and older. | Not studied in renal dysfunction. | Patients should be closely monitored. | C | Risk cannot be ruled out. |
| Budesonide/ formoterol | No dosage adjustment required, in the elderly population.<br><br>Approved for use in children ages 12 and older. | Not studied in renal dysfunction. | Patients should be closely monitored. | C | Risk cannot be ruled out. |

HFA=hydroflouroalkane.

## Adverse Drug Events

The most common adverse events associated with the fluticasone/salmeterol combination include upper respiratory infection and inflammation, pharyngitis, dysphonia, sinusitis, bronchitis, cough, headaches and nausea/vomiting. For the budesonide/formoterol combination they include nasopharyngitis, headache, upper respiratory infections, pharyngolaryngeal pain, and sinusitis.

**Table 6. Adverse Drug Events (%)[1-3,5,57]**

| Adverse Event | Fluticasone/Salmeterol | Budesonide/Formoterol |
|---|---|---|
| **Ear, Nose, and Throat** | | |
| Hoarseness/dysphonia | 2-5 | <3 |
| Nasopharyngitis | - | 9.7-10.5 |
| Pharyngitis | 10-13 | <3 |
| Pharyngolaryngeal pain | - | 6.1-8.9 |
| Sinusitis | 4-5 | 4.8-5.8 |
| Upper respiratory infection | 21-27 | 7.6-10.5 |
| Upper respiratory inflammation | 6-7 | - |
| **Lower Respiratory** | | |
| Bronchitis | 2-8 | <4 |
| Cough | 3-6 | <4 |
| **Neurology** | | |
| Headaches | 12-13 | 6.5-11.3 |

| Adverse Event | Fluticasone/Salmeterol | Budesonide/Formoterol |
|---|---|---|
| **Gastrointestinal** | | |
| Nausea/vomiting | 4-6 | 1.4-3.2 |

- Event not reported or incidence <1%.

**Contraindications/Precautions**[1-3]

Both fluticasone/salmeterol and budesonide/formoterol are contraindicated for the primary treatment of status asthmaticus or in any other acute asthma or chronic obstructive pulmonary disease (COPD) episodes where intensive measures might be required. Budesonide/formoterol is additionally contraindicated in patients with hypersensitivity to any ingredient that the combination product consists of, and fluticasone/salmeterol is further contraindicated in patients with severe milk protein hypersensitivities.

These agents are associated with a black box warning (outlined below) due to their long-acting $\beta_2$-agonist component (LABA). LABAs have been linked to an increased risk of asthma-related death. This association was first noted in a 28-week placebo-controlled trial that compared salmeterol to placebo. The study reported that salmeterol had significant occurrences of combined respiratory related deaths or respiratory related life-threatening experiences compared to placebo ($P$<0.05).[20] In a meta-analysis of 16 randomized controlled trials conducted by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations, and asthma-related deaths in adults and children when compared to placebo.[21] Due to these risks it is recommended that these agents only be used in patients not adequately controlled on other asthma-controller medications or in those patients whose disease severity warrants the use of two maintenance medications. Additionally, these medications at doses above the recommended amount can lead to significant cardiovascular adverse effects and potentially death. Patients should be advised not to use additional LABAs for any reason; furthermore these agents should also be used cautiously in patients with cardiovascular disorders due to their LABA component.

Another precaution is the systemic absorption of these agents which can potentially lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Particular attention should be placed on monitoring for the occurrence of adrenal suppression effects. If these effects do occur the patient's combination agent dose should be decreased in accordance with acceptable procedures. Additionally, when transferring patients from oral systemic corticosteroids to either fluticasone/salmeterol or budesonide/formoterol particular care is required as deaths due to adrenal insufficiency have occurred, as have the exacerbation of conditions previously controlled by systemic therapy, such as arthritis, rhinitis, eczema, etc.

Patients being treated with these agents have also, in rare cases, presented with systemic eosinophilia. Clinical features of the eosinophilia, such as vasculitis, can be consistent with Churg-Strauss syndrome. Health care providers should be alert to the presentation of eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and neuropathy in patients.

Bronchospams or an immediate increase in wheezing may occur after dosing with either agent. If bronchospams do occur they should be treated with a fast-acting inhaled bronchodilator.

When beginning treatment with either medication, it is advised that patients discontinue the use of their oral systemic corticosteroids and inhaled short-acting $\beta_2$-agonist (SABA) that are being used at a regular frequency (>4 times/day).

Patients who are being treated with these medications for prolonged periods have an increased risk of secondary infections due to immunosuppression. Viral infections such as chickenpox or measles can have a much more serious course in the susceptible adult or pediatric population. Particular care should be taken to avoid exposure in patients who have not had either of these diseases or have not been properly immunized. Furthermore these combination agents should be used with caution in patients with active or quiescent tuberculosis infection, untreated systemic fungal infections, bacterial, viral, or parasitic infections, or ocular herpes simplex. Additionally, health care providers should monitor patients for signs

and symptoms of pneumonia, specifically those patients using the combination agents for COPD treatment, as the use of these agents increases the risk for pneumonia development.

The use of long-term inhaled corticosteroids (ICS) also leads to the development of oropharyngeal fungal infections. Patients should be advised to rinse their mouth after inhalation of either agent. A decrease in bone mineral density has also been observed with long term inhaled corticosteroid treatment. Patients with major risk factors for decreased mineral content should be monitored and treated with the established standards of care. In the pediatric population inhaled corticosteroids can cause a decrease in growth velocity. Pediatric patients who are receiving ICS routinely should have their growth monitored. Close monitoring of patients with glaucoma and cataracts who are being treated with ICS is also recommended as increased intraocular pressure has been observed. Routine ocular examination should be considered in this patient population.

**Black Box Warning for Advair® for Risk of Asthma-Related Death**

| WARNING |
|---|
| Long-acting $\beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in Advair Diskus®, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe Advair® for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (Serevent® inhalation aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). |

**Black Box Warning for Symbicort® for Risk of Asthma-Related Death**

| WARNING |
|---|
| Long acting $\beta_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, Symbicort® should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting $\beta_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting $\beta_2$-adrenergic agonist), one of the active ingredients in Symbicort®. |

## Drug Interactions

**Table 7. Drug Interactions[1-3, 5, 39]**

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Budesonide, fluticasone | Azole antifungals (i.e. ketoconazole, fluconazole) | Azole antifungals may inhibit the metabolism of corticosteroids resulting in enhanced corticosteroid effects and toxicity. Doses of inhaled corticosteroids may need to be adjusted. |
| Formoterol, salmeterol | β-blockers | Pharmacologic effects of sympathomimetic $\beta_2$-agonists may be antagonized by β-blockers. Bronchospasms may occur. If possible, avoid coadministration of these agents. If a β-blocker is necessary, consider cautiously using a cardioselective β-blocker. |
| Formoterol, salmeterol | Monoamine oxidase inhibitors(MAOIs) | Salmeterol and formoterol are direct acting $\beta_2$-agonists, and should be administered cautiously in patients taking MAOIs or who have taken them within 2 weeks prior to the start of therapy. When these agents are given concurrently hypertensive crisis may occur. |

## Dosage and Administration

**Table 8. Dosing and Administration**[1-3,5,39]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Fluticasone/ salmeterol | Asthma:<br>Diskus: initial*, one inhalation of 100/50 µg or 250/50 µg twice daily; maintenance, one inhalation of 100/50 µg, 250/50 µg, or 500/50 µg twice daily<br><br>HFA MDI: initial*, two inhalations of 45/21 µg or 115/21 µg twice daily; maintenance, two inhalations of 45/21 µg, 115/21 µg, or 230/21 µg twice daily<br><br>Chronic obstructive pulmonary disease:<br>Diskus: initial, one inhalation of 250/50 µg twice daily; maintenance, one inhalation of 250/50 µg twice daily | Asthma:<br>Diskus: initial, one inhalation of 100/50 µg twice daily; maintenance, one inhalation of 100/50 µg twice daily<br><br>HFA MDI: initial, two inhalations of 45/21 µg or 115/21 µg twice daily; maintenance, two inhalations of 45/21 µg, 115/21 µg, or 230/21 µg twice daily | Diskus® (60 inhalations):<br>100/50 µg<br>250/50 µg<br>500/50 µg<br><br>HFA MDI (120 inhalations):<br>45/21 µg<br>115/21 µg<br>230/21 µg |
| Budesonide/ formoterol | Asthma:<br>MDI: initial, two inhalations twice daily of 80/4.5 µg or 160/4.5 µg; maintenance, two inhalations twice daily of 80/4.5 µg or 160/4.5 µg<br><br>Chronic obstructive pulmonary disease:<br>MDI: initial, two inhalation of 160/4.5 µg twice daily; maintenance, two inhalation of 160/4.5 µg twice daily | Asthma:<br>MDI: initial, two inhalations twice daily of 80/4.5 µg or 160/4.5 µg; maintenance, two inhalations twice daily of 80/4.5 µg or 160/4.5 µg | HFA MDI (60 and 120 inhalations):<br>80/4.5 µg<br>160/4.5 µg |

HFA=hydroflouroalkane, MDI=meter dose inhaler
* Initial dose listed above is indicated for patients not currently on an inhaled corticosteroid and whose treatment warrants the initiation of two maintenance therapies.

## Clinical Guidelines

**Table 9. Clinical Guidelines**

| Clinical Guidelines | Recommendations |
|---|---|
| The National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP): **Guidelines for the Diagnosis and Management of Asthma (2007)** [16] | Diagnosis<br>• To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction, and alternate diagnoses must be excluded.<br>• The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility, and additional studies to exclude alternate diagnoses.<br>• A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections, and symptoms that occur or worsen at night.<br>• Spirometry is needed to establish a diagnosis of asthma.<br>• Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing, and biomarkers of inflammation may be useful when considering alternative diagnoses. |

| Clinical Guidelines | Recommendations |
|---|---|
| | Treatment<br>• Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction.<br>• For initiating treatment, asthma severity should be classified, and the initial treatment should correspond to the appropriate severity category.<br>• Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma.<br>• Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing.<br>• Quick relief medications include short-acting $\beta_2$-agonists (SABAs), anticholinergics, and systemic corticosteroids.<br><br>Long-term Control Medications<br>• ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages.<br>• Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma.<br>• When patients ≥12 years of age require more than low-dose ICSs, the addition of a long-acting $\beta_2$-agonist (LABA) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists (LTRAs), theophylline, or in adults, zileuton.<br>• Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventative treatment prior to exercise or unavoidable exposure to known allergens.<br>• Omalizumab, an immunomodulator, is used as adjunctive therapy in patients ≥12 years old who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy.<br>• LTRAs (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.<br>• LABAs (salmeterol and formoterol) are not to be used as monotherapy for long-term control of persistent asthma.<br>• LABAs should continue to be considered for adjunctive therapy in patients ≥5 years of age who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.<br>• Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.<br>• Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma.<br><br>Quick-relief Medications<br>• SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise induced bronchospasm.<br>• There is inconsistent data regarding the superior efficacy of levalbuterol |

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
over albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.<br>
• Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.<br>
• Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.<br>
• The use of LABAs is not currently recommended to treat acute symptoms or exacerbations of asthma.<br><br>
Assessment, Treatment, and Monitoring<br>
• A stepwise approach to managing asthma is recommended to gain and maintain control of asthma in both the impairment and risk domains.<br>
• Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased use or SABA use >2 days a week for symptom relief generally indicates inadequate asthma control.<br>
• The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td>Preferred<br>SABA as needed</td><td>Preferred<br>Low-dose ICS<br><br>Alternative<br>Cromolyn, LTRA, nedocromil, or theophylline</td><td>Preferred<br>Low-dose ICS+LABA OR medium-dose ICS<br><br>Alternative<br>Low-dose ICS+either a LTRA, theophylline, or zileuton</td><td>Preferred<br>Medium-dose ICS+LABA<br><br>Alternative<br>Medium-dose ICS+either a LTRA, theophylline, or zileuton</td><td>Preferred<br>High-dose ICS+LABA AND consider omalizumab for patients who have allergies</td><td>Preferred<br>High-dose ICS+LABA+ oral steroid AND consider omalizumab for patients who have allergies</td></tr>
</table>
<br>
Management of Exacerbations<br>
• Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.<br><br>
Special Populations<br>
• For exercise induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. LTRAs may also attenuate exercise induced bronchospasm and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention however they are not as effective as SABAs. The addition of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm.<br>
• Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.<br>
• Albuterol is the preferred SABA in pregnancy because of an excellent safety profile.<br>
• ICSs are the preferred treatment for long-term control medication in pregnancy. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
</td></tr>
</table>

| Clinical Guidelines | Recommendations |
|---|---|
| Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention (2008)**[17] | Diagnosis<br>• A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness.<br>• Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity of airflow limitation, its reversibility, and its variability and provide confirmation of the diagnosis of asthma.<br><br>Treatment<br>• Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.<br>• Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible.<br>• Controller medications are administered daily on a long-term basis and include inhaled and systemic glucocorticosteroids, leukotriene modifiers, LABAs in combination with inhaled glucocorticosteroids, sustained-released theophylline, cromones, and anti-immunoglobulin E (IgE).<br>• Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled $\beta_2$-agonists, inhaled anticholinergics, short-acting theophylline, and SABAs.<br><br>Controller Medications<br>• Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages.<br>• Inhaled glucocorticosteroids differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences.<br>• To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids.<br>• Leukotriene modifiers are generally less effective than inhaled glucocorticosteroids therefore may be used as an alternative treatment in patients with mild persistent asthma.<br>• Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers.<br>• Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids.<br>• Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy.<br>• LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation.<br>• When a medium dose of an inhaled glucocorticosteroid fails to achieve control, the addition of a LABA is the preferred treatment.<br>• Controlled studies have shown that delivering a LABA and an inhaled glucocorticosteroid in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by a glucocorticosteroid.<br>• Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, |

| Clinical Guidelines | Recommendations |
|---|---|
| | this use is not approved by the Food and Drug Administration (FDA).<br>• Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on inhaled glucocorticosteroids alone.<br>• Cromolyn and nedocromil are less effective than a low dose of an inhaled glucocorticosteroid.<br>• Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed.<br>• Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE.<br>• Long-term oral glucocorticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects.<br>• Other anti-allergic compounds have limited effect in the management of asthma.<br><br><u>Reliever Medications</u><br>• Rapid-acting inhaled $\beta_2$-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages.<br>• Rapid-acting inhaled $\beta_2$-agonists should be used only on an as-needed basis at the lowest dose and frequency required.<br>• Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids, the use of this agent as a rescue inhaler is not approved by the FDA.<br>• Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled $\beta_2$-agonists.<br>• Short-acting theophylline may be considered for relief of asthma symptoms.<br>• Short-acting oral $\beta_2$-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse effects.<br>• Systemic glucocorticosteroids are important in the treatment of severe acute exacerbations.<br><br><u>Assessment, Treatment, and Monitoring</u><br>• The goal of asthma treatment is to achieve and maintain clinical control.<br>• To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.<br>• Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.<br>• Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment. |

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
<ul><li>The management approach based on control is outlined below:</li></ul>
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting $\beta_2$-agonist</td></tr>
<tr><td rowspan="5">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose inhaled glucocortico-steroid</td><td colspan="2">Low-dose inhaled glucocorticosteroid +LABA</td><td>Medium- or high-dose inhaled glucocortico-steroid+LABA</td><td>Oral glucocortico-steroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose inhaled glucocorticosteroid</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroids +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroid +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>
<u>Management of exacerbations</u>
<ul>
<li>Repeated administration of rapid-acting inhaled $\beta_2$-agonists is the best method of achieving relief for mile to moderate exacerbations.</li>
<li>Systemic glucocorticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled $\beta_2$-agonists or if the episode is severe.</li>
</ul>
<u>Special Populations</u>
<ul>
<li>LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formeterol is more suitable for symptom relief as well as symptom prevention over salmeterol.</li>
<li>Appropriately monitored use of theophylline, inhaled glucocorticosteroids, $\beta_2$-agonists, and leukotriene modifiers, specifically montelukast, are not associated with an increased incidence of fetal abnormalities.</li>
<li>Inhaled glucocorticosteroids have been shown to prevent exacerbations of asthma during pregnancy.</li>
<li>Acute exacerbations during pregnancy should be treated with nebulized rapid-acting $\beta_2$-agonists and oxygen. Systemic glucocorticosteroids should be instituted when necessary.</li>
</ul>
</td></tr>
<tr><td>Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (COPD) (2008)[18]</td><td>
<u>Diagnosis</u>
<ul>
<li>A clinical diagnosis of COPD should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking.</li>
<li>A diagnosis of COPD should be confirmed by spirometry.</li>
<li>COPD patients typically display a decrease in both Forced Expiratory Volume in one second ($FEV_1$) and $FEV_1$/ Forced Vital Capacity (FVC) ratio.</li>
<li>The presence of a post-bronchodilator $FEV_1/FVC<0.70$ and $FEV_1<80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.</li>
<li>A detailed medical history should be obtained for all patients suspected of developing COPD.</li>
<li>Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.</li>
<li>Bronchodilator reversibility testing should be performed to rule out the possibility of asthma.</li>
</ul>
</td></tr>
</table>

| Clinical Guidelines | Recommendations |
|---|---|
| | • Chest radiograph may be useful to rule out other diagnoses.<br>• Arterial blood gas measurements should be performed in advanced COPD.<br>• Screening for $\alpha_1$-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger.<br>• Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis.<br><br>Treatment<br>• Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures.<br>• The management of COPD should be individualized to address symptoms and improve the patient's quality of life.<br>• None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications.<br>• Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations.<br>• Principle bronchodilators include $\beta_2$-agonists, anticholinergics and theophylline used as monotherapy or in combination.<br>• The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.<br>• For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators.<br>• Inhaled corticosteroids should be used in patients with an $FEV_1$<50% of the predicted value.<br>• Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio.<br>• COPD patients should receive an annual influenza vaccine.<br>• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an $FEV_1$<40% of the predicted value.<br>• Exercise training programs should be implemented for all COPD patients.<br>• Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure.<br><br>Management of Exacerbations<br>• The most common causes of an exacerbation are bronchial tree infections and air pollution.<br>• Inhaled $\beta_2$-agonists, with or without anticholinergics, and systemic corticosteroids are effective treatments for exacerbations of COPD.<br>• Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment. |
| National Institute for Clinical Excellence (NICE): **COPD: National Guideline on the Management of COPD in Adults in Primary and** | Diagnosis<br>• Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD.<br>• The primary risk factor is smoking.<br>• Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as $FEV_1$<80% predicted and $FEV_1$/FVC<70%. |

| Clinical Guidelines | Recommendations |
|---|---|
| **Secondary Care (2004)**[19] | Treatment<br>• Smoking cessation should be encouraged for all patients with COPD.<br>• Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation.<br>• Long-acting bronchodilators ($\beta_2$-agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators, if two or more exacerbations occur per year.<br>• Inhaled corticosteroids should be added to patients on long-acting bronchodilators to decrease the frequency of exacerbations in patients with an $FEV_1 \leq 50\%$ of the predicted value.<br>• Oral corticosteroids should be reserved for those patients with advanced COPD.<br>• Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Plasma levels must be measured since there is a larger side effect burden with theophylline.<br>• Pulmonary rehabilitation should be made available to patients.<br>• Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure.<br><br>Management of Exacerbations<br>• Patients with exacerbations should be evaluated for hospital admission.<br>• Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial.<br>• Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days.<br>• Oxygen should be given to maintain oxygen saturation above 90%.<br>• Patients should receive invasive and noninvasive ventilation as necessary.<br>• Respiratory physiotherapy may be used to help remove sputum.<br>• Before discharge, patients should be evaluated by spirometry.<br>• Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional. |

**Conclusions**

The combination inhaled corticosteroid (ICS) and long-acting $\beta_2$-agonist (LABA) agents are Food and Drug Administration (FDA) approved for the treatment of asthma in adults and children (age varies depending on product) as well as for the treatment of chronic obstructive pulmonary disease (COPD). The individual components are also commercially available.

Current national and international guidelines support the use of these combination products for long-term control and prevention of symptoms in adults and children older than five years of age if they have not had sufficient symptom control with an ICS. In children younger than five a LABA and ICS combination is recommended after the patient has failed a trial of both a low and medium dose ICS. A major divergence between the two guidelines, the National, Heart, Lung, Blood Institute (NHLBI) and Global Initiative for Asthma (GINA), is the recommendation of the Symbicort® Maintenance and Reliever Therapy (SMART) dosing regimen by the GINA guidelines. Conversely, the NHLBI guidelines recommend that LABAs should not be used for the treatment of acute asthma symptoms or exacerbation.[16-17] In regards to the COPD consensus guidelines both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and NICE guidelines recommend the use of these combination agents as second-line, when a patient has failed an initial short and long-acting bronchodilator.[18-19]

In regards to the clinical efficacy of these agents, studies have demonstrated that the combination products are superior to the individual separate components; furthermore head to head trials comparing the combination products have not demonstrated that one of the agents is consistently superior over the other. Additionally, these agents have also been compared to the SMART dosing regimen. The SMART dosing regimen used in these studies demonstrated a greater decrease in asthma exacerbations and hospitalization rates than either of the two standard dosing combination agents. It is important to note however that this dosing regimen has not been approved by the FDA and is therefore not considered standard therapy. Furthermore, the NHLBI guidelines specifically recommend that long-acting $\beta_2$-agonists should not be used for acute asthma symptoms or exacerbations. Additionally none of the asthma or COPD guidelines recommend one combination agent over the other; further reinforcing the lack of any significant clinical difference between these two agents.[6-15, 20-56]

## Recommendations

In recognition of the well-established role of the inhaled corticosteroid and long-acting $\beta_2$-agonist combination agents for the treatment of asthma, and chronic obstructive pulmonary disease (COPD), as well as their equivalent efficacy, and safety in the management of both disease states, cost considerations, and the lack of availability of either combination agent as a generic entity, no changes are recommended to the current approval criteria.

Inhaled corticosteroid/long-acting $\beta_2$-agonist combination products (Advair® Discus, Advair® HFA, Symbicort®) are all preferred on the OVHA Preferred Drug List (PDL) and do not require prior authorization for approval.

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